

# Improving physical realism, stereochemistry and side-chain accuracy in homology modeling

Krieger *et al.*, Proteins (2009)

# Outline



Motivation & Introduction

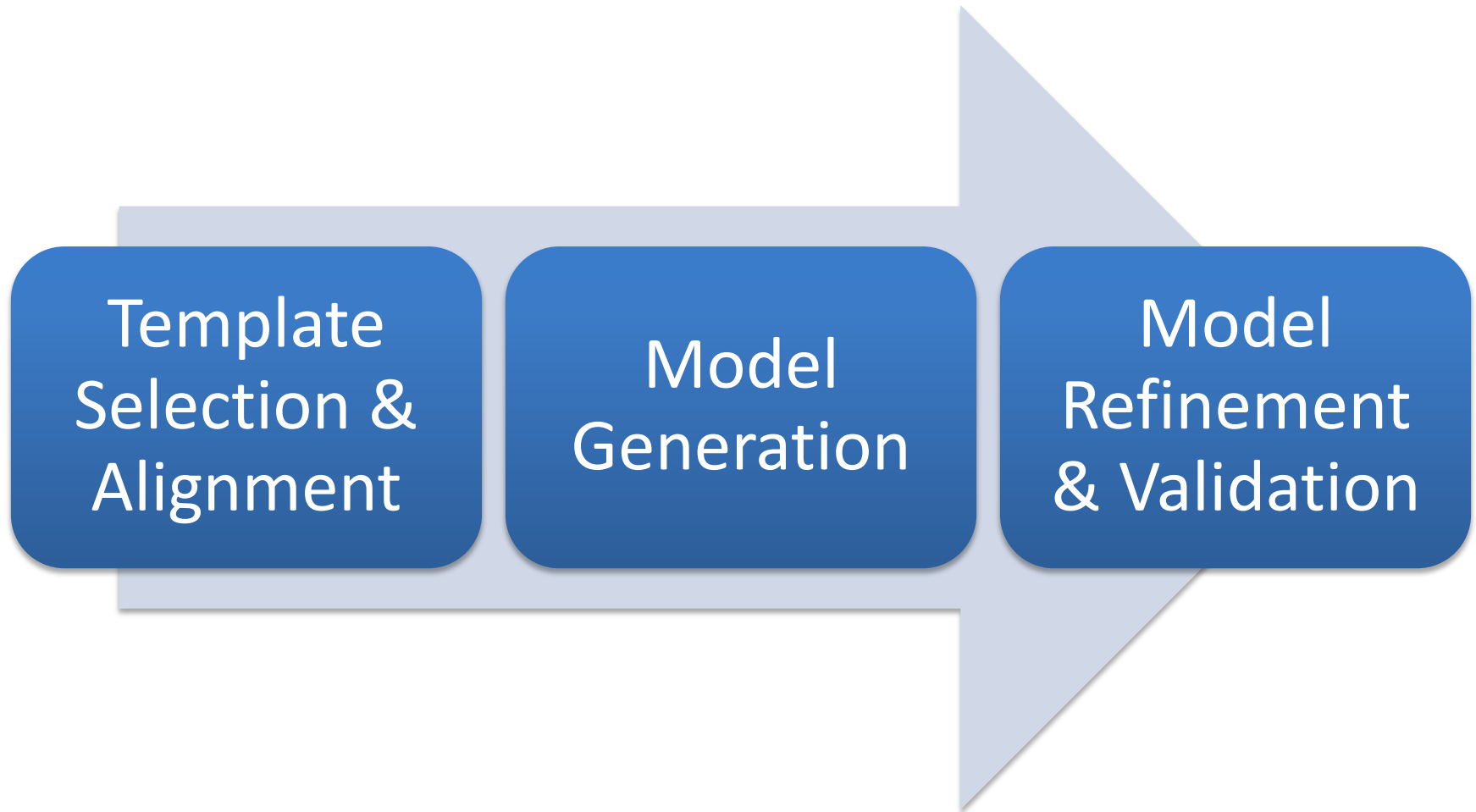


Four Well-Performing Approaches in CASP 8:  
*YASARA, LEE, Rosetta & undertaker*



Conclusion

# Physically realistic models are the goal of model refinement



# There are two basic approaches for correct model generation

“correct by construction”

- ensure correct parameters in the beginning
- no harmful changes later on

optimization  
of cost  
functions

- accuracy: realism, conflicting terms
- efficiency: search in conformational space

# The ideal method does not exist

## physical force fields

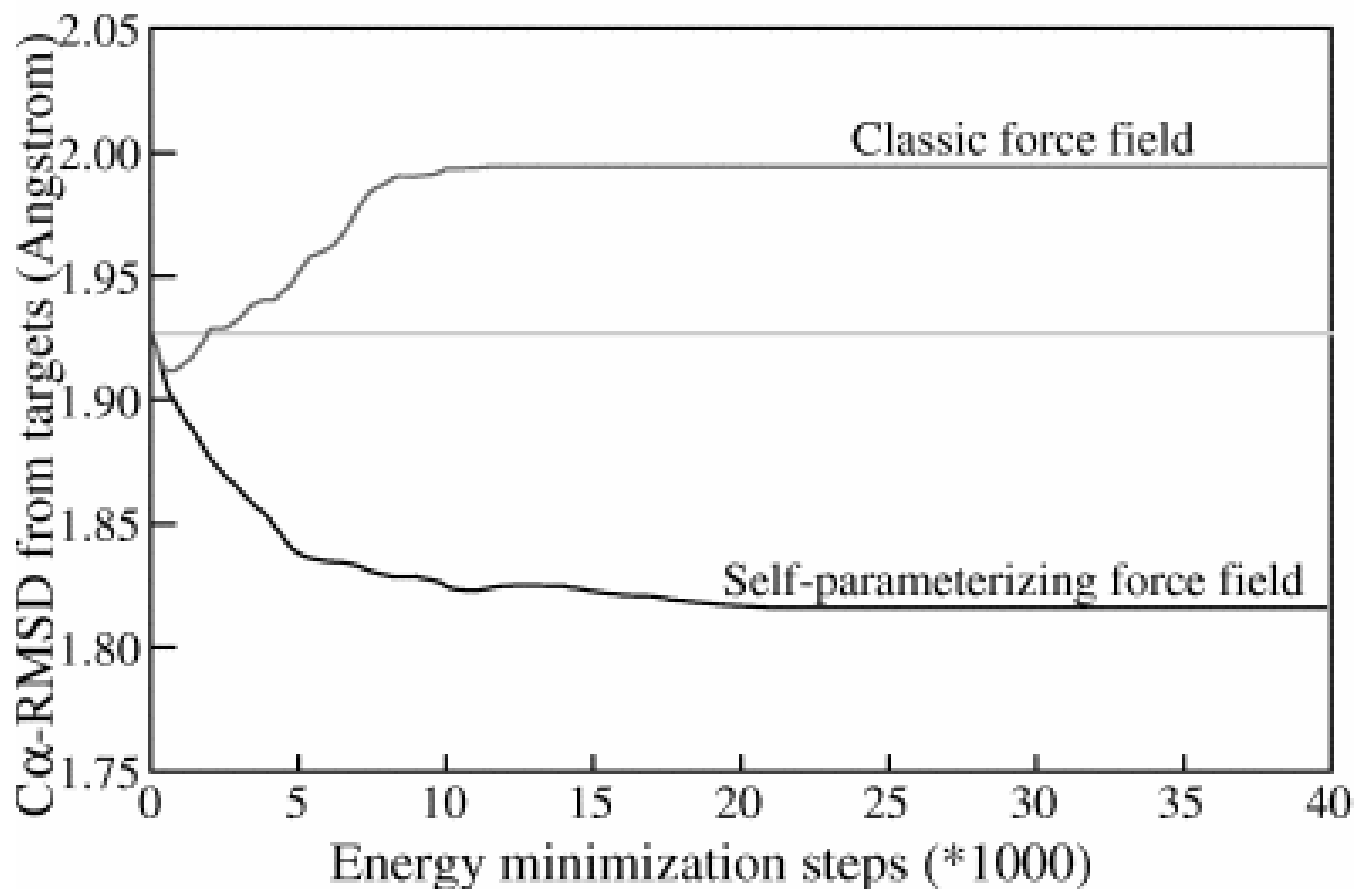
- physical interactions
- AMBER, CHARMM
- computationally expensive
- accurate?

## empirical force fields

- knowledge-based (Inverse Boltzmann Law)
- too crude
- artificially good-looking models?

+ how to search space efficiently?

# Model refinement may decrease quality measures



How to overcome those  
problems?

# YASARA tries to minimize damage to crystal structures

## damage minimization

- energy-minimize set of 25 crystal structures
- parameter change
- measure damage
- accept/reject

## combined force field

- physical (AMBER)
- knowledge-based torsional potentials (1D, 2D, 3D)



# LEE performs rigorous optimization

## restraint information

- incorporate many templates
- competing terms
- frustrated energy function

## extensive optimization

- conformational space annealing (*Modeller-CSA*)
- search for global maximum in energy landscape
- also for MSA and side-chains

# Rosetta effectively samples with a realistic force field

## physical realism

- all-atom force field
- explicit backbone & side-chain interactions
- H-bond potentials
- hydrophobic effect
- knowledge-based torsional angle potentials

## effective sampling

- initial large-scale low-resolution sampling
- Monte Carlo *minimization*
- “hopping” by rotamer conformations
- random rebuild of loops & variable regions
- ...

# undertaker assembles good fragments and optimizes

## good candidate pool

- random all-atom conformation
- complete models from templates
- combines both
- highest scoring: seed for genetic algorithm

## genetic optimization

- genetic algorithm
- empirical cost function
- 0-1 potential for clash detection
- bond-preserving operators

# Conclusion

- various approaches, no more “frozen core”
- models physically more realistic
- no considerable quality improvement (RMSD)
- no decrease of quality any more w.r.t real structure
- differences hard to measure
- importance & influence of alignments

# References

Krieger E, Joo K, Lee J *et al.*:

Improving physical realism, stereochemistry, and side-chain accuracy in homology modeling: Four approaches that performed well in CASP8.

*Proteins* 2009;77 Suppl 9(S9):114-22.